REGULAR ARTICLE

blood advances

Maximum tumor diameter is associated with relapse risk in limited-stage Hodgkin lymphoma: an international study

Elizabeth H. Phillips,[1,2,*] Nicholas Counsell,[3,*] Tim Illidge,[1,4] Marc Andre,[5] Igor Aurer,[6] Valeria Fiaccadori,[7,8] Catherine Fortpied,[7] Anouk Neven,[7,9] Massimo Federico,[10] Sally F. Barrington,[11] John Raemaekers,[12] and John Radford[1,2]

[1]Division of Cancer Sciences, University of Manchester and Manchester Academic Health Science Centre, Manchester, United Kingdom; [2]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom; [3]Cancer Research UK and University College London Cancer Trials Centre, Cancer Institute, University College London, London, United Kingdom; [4]Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom; [5]Department of Haematology, Centre Hospitalier Universitaire, Université Catholique de Louvain Namur, Yvoir, Belgium; [6]Division of Hematology, Department of Internal Medicine, University Hospital Centre Zagreb, and Medical School, University of Zagreb, Zagreb, Croatia; [7]Department of Statistics, European Organisation for the Research and Treatment of Cancer, Brussels, Belgium; [8]Department of Hematology, University College London Hospital, London, United Kingdom; [9]Competence Center for Methodology and Statistics, Luxembourg Institute of Health, Strassen, Luxembourg; [10]CHIMOMO Department, University of Modena and Reggio Emilia, Modena, Italy; [11]King's College London and Guy's and St Thomas' PET Centre, School of Biomedical Engineering and Imaging Sciences, King's College London, King's Health Partners, London, United Kingdom; and [12]Radboud University Medical Center, Nijmegen, The Netherlands

Key Points

- Increasing MTD is strongly associated with increased risk of relapse in limited-stage HL.
- MTD and treatment with chemotherapy alone are independent risk factors; patients with both risk factors had suboptimal event-free survival.

Tumor bulk is an established prognostic factor in Hodgkin lymphoma (HL), but most patients with limited-stage (LS) HL do not have "bulk" by standard definitions. In the RAPID trial, maximum tumor diameter (MTD) was associated with relapse risk in LS-HL patients achieving positron emission tomography negativity (PET-) after doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). We aimed to externally validate these findings in the H10 trial. Stage I/IIA HL patients, without mediastinal bulk, who achieved PET- with ABVD were included. Patients received 3 ABVD plus radiotherapy (n = 208) or 3 ABVD alone (n = 211) in RAPID, and 3 to 4 ABVD plus radiotherapy (n = 556) or 4 to 6 ABVD alone (n = 303) in H10. MTD was strongly associated with event-free survival (relapse or HL-related death) in H10 (hazard ratio [HR], 1.22; 95% confidence interval [CI], 1.07-1.38; P = .003), a similar effect to that seen in RAPID (HR, 1.19; 95% CI, 1.02-1.39; P = .02), giving an estimated 21% risk increase per centimeter MTD (HR_{pooled}, 1.21; 95% CI, 1.09-1.33; P < .001). Effect sizes were similar for patients treated with ABVD alone and ABVD plus radiotherapy, with no differential effect ($p_{interaction}$ = 0.97). Treatment modality and MTD were independent risk factors; patients with higher MTD receiving chemotherapy alone had the greatest relapse risk. This international validation study confirms MTD is strongly associated with relapse risk in patients with LS-HL achieving PET- and informs decision-making around risk-adapted application of radiotherapy. The trials were registered at www.clinicaltrials.gov as #NCT00943423 and #NCT00433433.

Submitted 21 October 2024; accepted 17 December 2024; prepublished online on *Blood Advances* First Edition 7 January 2025. https://doi.org/10.1182/bloodadvances.2024015140.

*E.H.P. and N.C. contributed equally to this study.

Requests for data should be directed to the RAPID and H10 trial teams separately, or contact the corresponding author, Elizabeth H. Phillips (beth.phillips@manchester.ac.uk) in the first instance.

The full-text version of this article contains a data supplement.

Introduction

Very high cure rates are achieved for patients with limited-stage (LS) classical Hodgkin lymphoma (HL) treated with modern combined chemotherapy-radiotherapy approaches.[1-3] However, late toxicity from treatment is a major cause of excess morbidity and mortality in survivors, particularly increased rates of second malignancies and cardiovascular disease.[4,5] Therefore, reducing treatment burden is a major priority in LS-HL. Risk-adapted treatment is key to achieving this, allowing deescalation for low-risk patients while maintaining high cure rates, but success is dependent on accurate risk stratification.

Traditionally, treatment selection in LS-HL has been based on the presence of clinical risk factors, according to the European Organisation for Research and Treatment of Cancer (EORTC) or German Hodgkin Study Group criteria. More recently, ^{18}F-fluorodeoxyglucose positron emission tomography (PET) response to chemotherapy has consistently been associated with outcomes and become established in routine clinical practice.[6,7] PET response-adapted treatment strategies have been increasingly adopted and may have reduced the prognostic value of pretreatment clinical risk stratification.[6] However, attempts to deescalate treatment and omit radiotherapy based on early PET response have met with mixed success, with an increase in relapse rates of 4% to 12% in patients achieving PET negativity.[1,2,8] The negative predictive value of PET response is suboptimal, with more than half of relapses occurring in patients who are PET negative, irrespective of treatment modality.[2,3] Therefore, further improvements in predictive biomarkers are required to inform more precise application of risk-adapted therapy in LS-HL.

The size of tumor masses is a well-established prognostic factor in HL.[9-12] Tumor "bulk" in HL was originally defined by the Cotswold report in 1989 to encompass mediastinal masses of more than one-third of the internal transverse diameter of the thorax at the level of T5/6 on posteroanterior chest X-ray and masses of ≥10 cm elsewhere.[13] Despite advances in lymphoma staging with PET, evolution of treatment pathways, and the introduction of response-adapted therapy, the Cotswold definition is still widely used to this day.[14] In particular, the presence of mediastinal bulk is incorporated into pretreatment clinical risk stratification in LS-HL.[8,15] However, the majority of patients with LS-HL do not meet traditional definitions of tumor bulk.[8] Furthermore, the relevance of tumor bulk has not been evaluated in the context of PET-directed treatment.

We previously evaluated the role of tumor diameter outside of conventional definitions of bulk in LS-HL for patients receiving PET-adapted therapy in the UK National Cancer Research Institute RAPID trial. We demonstrated that baseline maximum tumor diameter (MTD) is independently associated with event-free survival (EFS) and progression-free survival (PFS) in patients with LS-HL who had a negative PET scan after ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy. HL relapse risk increased by 19% per cm increase in baseline MTD (hazard ratio [HR], 1.19; 95% confidence interval [CI], 1.02-1.39; $P = .02$).[11] The aim of this study was to validate these findings by assessing the prognostic association of MTD in an external cohort of patients with LS-HL recruited to the EORTC/Fondazione Italiano Linfomi/Lymphoma Study Association H10 trial,[8] and to explore the influence of treatment modality.

Patients and methods

Discovery cohort: RAPID trial

RAPID was a randomized controlled, phase 3, noninferiority trial comparing ABVD chemotherapy alone (C) with combined modality therapy (ABVD plus involved-field radiotherapy [CMT]) in patients with LS-HL achieving PET negativity after 3 cycles of ABVD. The trial design and procedures have been published previously.[2] Briefly, eligible patients were aged 16 to 75 years with newly diagnosed, histologically confirmed stage IA or IIA HL, and no mediastinal bulk (≥33% of the internal thoracic diameter at T5-T6). In total, 602 patients were recruited, of whom 571 had a centrally reviewed PET; 426 patients achieved PET negativity (equivalent to Deauville score of 1-2) and were eligible to be randomized. Six PET-negative patients withdrew before randomization, and 1 additional patient has been excluded, when review of original diagnostic material at relapse identified a non-HL diagnosis. Therefore, 419 RAPID patients are included (211 C and 208 CMT; Figure 1).

Validation cohort: H10 trial

H10 was a randomized controlled, phase 3, noninferiority trial, comparing CMT with a PET-directed approach, whereby patients achieving PET negativity after 2 cycles of ABVD completed further chemotherapy treatment without radiotherapy. The trial design and procedures have been published previously.[8] In brief, eligible patients were aged 15 to 70 years with newly diagnosed, supradiaphragmatic stage I or II classical HL. Patients who were PET negative according to the International Harmonization Project criteria[16] (ie, largely Deauville score 1-2) received either 4 to 6 cycles of ABVD (540 C) or 3 to 4 cycles of ABVD plus involved-node radiotherapy (1024 CMT), with the duration of ABVD determined by baseline EORTC risk stratification. Randomization was halted after an interim analysis demonstrated futility with all subsequent patients enrolled receiving CMT. In total, 687 patients had mediastinal bulk and/or B symptoms and would have been ineligible for RAPID so are excluded from this validation cohort. Thus, 877 H10 patients are included in the current analysis (311 C and 566 CMT; Figure 1).

Assessment of clinical risk factors

For both trials, bidimensional baseline tumor dimensions (in cm) were evaluated by CT, reported by local radiologists, and prospectively collected at trial entry. The larger of these dimensions was taken as baseline MTD. Use of IV contrast was mandated in the H10 protocol, and was used according to local standards in RAPID. Data on MTD were missing for 18 RAPID-eligible patients recruited to the H10 trial. Baseline clinical risk factors were collected prospectively to allow stratification according to EORTC risk group, including age, mediastinal-thoracic ratio, B symptoms, erythrocyte sedimentation rate, and number of involved nodal areas.

Statistical considerations

The primary objective of this study was to externally validate the prognostic value of MTD in patients with LS-HL recruited to the H10 trial. The primary end point was HL-related EFS, defined as relapse or HL-related death; censoring deaths from treatment toxicity or causes unrelated to HL. Patients were censored at the

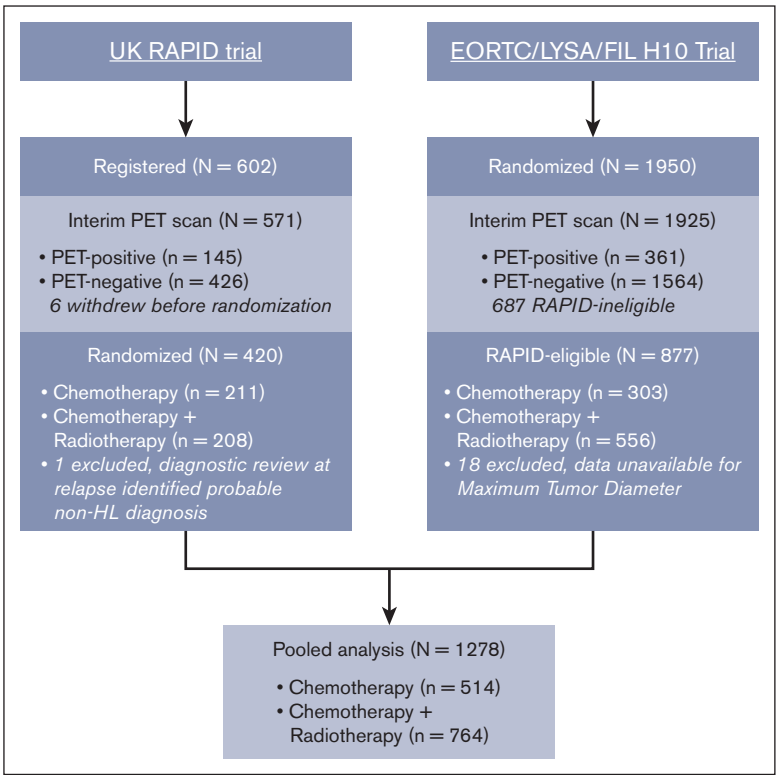


Figure 1. CONSORT flow diagram.

date last seen if no event was observed. Secondary objectives included describing the association with MTD by treatment modality (ie, C or CMT), and the association of MTD with PFS (progression or death due to any cause). There were too few events to explore associations with overall survival (RAPID: 1 HL and 10 non-HL deaths, H10: 3 HL and 5 non-HL deaths).

The associations of baseline MTD with EFS and PFS were described using the Kaplan-Meier method, analyzed using multivariable Cox regression analyses and model assumptions of proportional hazards and linearity of MTD were checked. Firstly, associations with MTD were assessed adjusting for treatment arm, to account for differences in trial design including number of ABVD cycles, and then also adjusting for baseline risk stratification by EORTC criteria (missing for 51 RAPID patients) in multivariable analyses. Finally, after independent validation was confirmed, data from RAPID and H10 were pooled to provide more precise estimates for the associations with MTD, adjusting for trial population and treatment arm to account for trial design. These associations were also investigated within treatment groups (ie, C or CMT), and via tests of interaction. In exploratory analyses, MTD was dichotomized using increasing 1-cm intervals to investigate the utility of different MTD thresholds by assessing effect sizes and performance via time-dependent receiver operating characteristic curves.

Data analyses were performed using SAS software, version 9.4 (SAS Institute), and GraphPad Prism, version 9.3.1 for Windows (www.graphpad.com).

RAPID was approved by the UK multicenter research ethics committee; H10 was approved by national ethics committees in all participating countries (France, Belgium, Italy, and The Netherlands).

Results

External validation of MTD

The baseline characteristics for patients achieving PET negativity on RAPID and H10 (without B symptoms or mediastinal bulk) are shown by trial arm in Table 1. Generally, MTD was higher in H10 than RAPID (median, 3.9 vs 3.0 cm, respectively). Also, patients were marginally younger (median, 32 vs 34 years), with a higher proportion of stage II disease (71.4 vs 66.8%), erythrocyte sedimentation rate of >50 (14.3 vs 11.9%), and extranodal disease (2.7 vs 0.2%) in H10 than RAPID. Baseline EORTC risk groups were similar in the 2 trials (66.8 vs 65.2% favorable, respectively).

After a median follow-up of 4.5 years in the H10 validation cohort of RAPID-eligible patients, 38 HL relapse events (27 C and 11 CMT), 3 HL-related deaths (3 C and 0 CMT), and 5 non-HL deaths (2 C and 3 CMT) have been observed. Non-HL deaths were censored in the primary analysis of EFS but included as events for the secondary analysis of PFS.

For H10 patients that were RAPID eligible, we found a clear association between MTD (in centimeters) and EFS (n = 859; HR, 1.22; 95% CI, 1.07-1.38; $P = .003$; Table 2), similar to that observed in RAPID (n = 419; HR, 1.19; 95% CI, 1.02-1.39; $P = .02$). Results in the H10 validation cohort were consistent when adjusted for number of chemotherapy cycles (HR, 1.24; 95% CI, 1.09-1.42; $P = .001$) and EORTC risk stratification (HR, 1.22; 95% CI, 1.07-1.39; $P = .003$) in multivariable analyses. There was no evidence of an association between MTD and EFS for RAPID-ineligible H10 patients (ie, B symptoms and/or mediastinal bulk present) with available MTD data (n = 672; HR, 1.03; 95% CI, 0.96-1.11; $P = .37$).

Table 1. Baseline characteristics for patients achieving PET negativity in RAPID and H10 subset (excluding stage III/IV, B symptoms, and mediastinal bulk)

Baseline characteristic	RAPID PET-negative CMT group (n = 208)	RAPID PET-negative C group (n = 211)	RAPID PET-negative Total (N = 419)	H10 PET-negative CMT group (n = 566)	H10 PET-negative C group (n = 311)	H10 PET-negative Total (N = 877)
MTD in cm, median (interquartile range)	3.0 (1.8-4.5)	3.0 (2.0-4.0)	3.0 (1.9-4.3)	3.9 (2.9-5.2) (10 missing)	3.8 (2.7-5.0) (8 missing)	3.9 (2.8-5.1) (18 missing)
Age in years, median (interquartile range)	34 (25-48)	34 (25-47)	34 (25-47)	32 (24-44)	31 (24-44)	32 (24-44)
Age in years, n (%)						
<50	160 (76.9%)	166 (78.7%)	326 (77.8%)	475 (83.9%)	264 (84.9%)	739 (84.3%)
≥50	48 (23.1%)	45 (21.3%)	93 (22.2%)	91 (16.1%)	47 (15.1%)	138 (11.7%)
Sex, n (%)						
Female	106 (51.0%)	104 (49.3%)	210 (50.1%)	282 (49.8%)	160 (51.4%)	442 (50.4%)
Male	102 (49.0%)	107 (50.7%)	209 (49.9%)	284 (50.2%)	151 (48.6%)	435 (49.6%)
Stage, n (%)						
I	69 (33.2%)	70 (33.2%)	139 (33.2%)	154 (27.2%)	97 (31.2%)	251 (28.6%)
II	139 (66.8%)	141 (66.8%)	280 (66.8%)	412 (72.8%)	214 (68.8%)	626 (71.4%)
ESR of >50, n (%)	20 (11.8%)	22 (12.1%)	53 (11.9%)	89 (15.7%)	36 (11.6%)	125 (14.3%)
Extranodal disease, n (%)	0 (0.0%)	1 (0.5%)	1 (0.2%)	15 (2.7%) (14 missing)	8 (2.6%) (6 missing)	23 (2.7%) (20 missing)
No. of nodal areas, n (%)						
≥3 involved	64 (30.8%)	61 (28.9%)	125 (29.8%)	190 (33.6%)	89 (28.6%)	279 (31.8%)
≥4 involved	19 (9.1%)	22 (10.4%)	41 (9.8%)	39 (6.9%)	20 (6.4%)	59 (6.7%)
EORTC criteria, n (%)						
Favorable	118 (64.5%)	122 (65.9%)	240 (65.2%)	371 (65.5%)	215 (69.1%)	586 (66.8%)
Unfavorable	65 (35.5%)	63 (34.1%)	128 (34.8%)	195 (34.5%)	96 (30.9%)	291 (33.2%)

cm, centimeter; ESR, erythrocyte sedimentation rate.

Similar results were observed when including the 5 non-HL deaths in analyses of PFS, as expected, given the small number of these events (supplemental Table). There was a clear association between MTD in centimeters and PFS (n = 859; HR, 1.22; 95% CI, 1.08-1.37; $P = .001$), as well as when adjusted for number of chemotherapy cycles (HR, 1.24; 95% CI, 1.10-1.41; $P = .001$) and EORTC risk stratification (HR, 1.21; 95% CI, 1.08-1.37; $P = .002$).

MTD and treatment modality

For RAPID-eligible H10 patients receiving chemotherapy alone, we again found a similar association between MTD and EFS (n = 303; HR, 1.19; 95% CI, 1.01-1.40; $P = .03$), as observed in RAPID (n = 211; HR, 1.20; 95% CI, 0.99-1.44; $P = .06$). Results were consistent when adjusted for number of chemotherapy cycles and EORTC risk stratification in multivariable analyses, and similar associations were observed for PFS.

For RAPID-eligible H10 patients receiving CMT, there was also an association between MTD and EFS, although only 11 HL events were observed (n = 556; HR, 1.27; 95% CI, 1.04-1.56; $P = .02$). There were only 9 HL events in RAPID patients receiving CMT but a similar association with EFS was observed (n = 208; HR, 1.19; 95% CI, 0.92-1.55; $P = .19$), although this was not statistically significant. Again, results were consistent when adjusted for number of chemotherapy cycles and EORTC risk stratification, and in analyses of PFS.

Pooled analyses of RAPID and H10 data

Given the observed consistency in results between the RAPID discovery cohort and the H10 validation cohort, a pooled analysis was carried out to provide more precise estimates on the role of MTD with a larger number of events (Figure 2; Table 2). For all RAPID-eligible patients (C and CMT), adjusting for trial cohort and treatment group in multivariable analyses, we found a 21% increase in HL relapse risk per centimeter increase in MTD at baseline (n = 1278; pooled HR, 1.21; 95% CI, 1.09-1.33; $P < .001$).

In patients receiving chemotherapy alone, we found a 19% increase in HL relapse risk per centimeter increase in MTD at baseline (n = 514; pooled HR, 1.19; 95% CI, 1.01-1.35; $P = .005$), with no clear MTD threshold above which we could identify a marked difference in EFS. An MTD threshold of 5 cm (area under the curve [AUC] = 60.0%) performed marginally better than MTD thresholds of 4, 3, and 6 cm (AUCs = 59.2%, 58.5%, and 56.7%, respectively) in time-dependent receiver operating characteristic curve analyses (Table 3; supplemental Figure). Five-year EFS rates for patients receiving chemotherapy alone with MTD of <5 cm and MTD of ≥5 cm were 92.4% (95% CI, 89.1-94.7) and 82.3% (95% CI, 73.8-88.2), respectively.

In an exploratory pooled analysis of RAPID-eligible patients treated with CMT, MTD was associated with EFS (n = 764; HR, 1.24; 95% CI, 1.05-1.46; $P = .009$); with only 20 events in this group, it was not possible to fully evaluate MTD thresholds. However, EFS

Table 2. Association between (MTD, per centimeter) and EFS for patients achieving PET negativity: H10 subset and pooled analysis of H10 subset with RAPID

Association between MTD and EFS in multivariable analyses	HR (95% CI), *P* value
H10 PET negative, all patients (N = 859 with 41 EFS events, 18 missing MTD)	
Adjusting for treatment group (ie, C or CMT)	1.22 (95% CI, 1.07-1.38), .003
Adjusting for treatment arm (ie, C or CMT, and cycles)	1.24 (95% CI, 1.09-1.42), .001
Adjusting for treatment group and EORTC risk group	1.22 (95% CI, 1.07-1.39), .003
H10 PET negative, C group (N = 303 with 30 EFS events, 8 missing MTD)	
Unadjusted	1.19 (95% CI, 1.01-1.40), .03
Adjusting for treatment arm (ie, cycles)	1.22 (95% CI, 1.03-1.45), .02
Adjusting for EORTC risk group	1.21 (95% CI, 1.02-1.44), .03
H10 PET negative, CMT group (N = 556 with 11 EFS events, 10 missing MTD)	
Unadjusted	1.27 (95% CI, 1.04-1.56), .02
Adjusting for treatment arm (ie, cycles)	1.29 (95% CI, 1.04-1.59), .02
Adjusting for EORTC risk group	1.28 (95% CI, 1.04-1.57), .02
Pooled PET negative, all patients (N = 1278; 71 EFS events)	
Adjusting for trial and treatment group (ie, C or CMT)	1.21 (95% CI, 1.09-1.33), <.001
Adjusting for trial and treatment arm (ie, C or CMT, and cycles)	1.22 (95% CI, 1.10-1.35), <.001
Adjusting for trial, treatment group and EORTC risk group*	1.18 (95% CI, 1.06-1.30), .002
Pooled PET negative, C group (N = 514; 51 EFS events)	
Adjusting for trial	1.19 (95% CI, 1.01-1.35), .005
Adjusting for trial and treatment arm (ie, cycles)	1.21 (95% CI, 1.06-1.37), .004
Adjusting for trial and EORTC risk group	1.15 (95% CI, 1.01-1.32), .040
Pooled PET negative, CMT group (N = 764; 20 EFS events)	
Adjusting for trial	1.24 (95% CI, 1.05-1.46), .009
Adjusting for trial and treatment arm (ie, cycles)	1.25 (95% CI, 1.06-1.47), .009
Adjusting for trial and EORTC risk group	1.25 (95% CI, 1.06-1.47), .007

cm, centimeter.
*51 RAPID patients missing EORTC risk group: 26 in the C group and 25 in the CMT group.

rates were high irrespective of MTD; using a median split in the CMT group, 5-year EFS rates were 96.3% with MTD of <3.6 cm and 97.7% with MTD of ≥3.6 cm, respectively.

There was no evidence of a differential effect for MTD between treatment modalities (interaction, $P = .97$), and the CIs for each include the overall effect estimate for MTD. Kaplan-Meier plots of EFS according to MTD and treatment modality are shown in Figure 3.

Discussion

This international validation study confirms the association between baseline MTD and relapse risk for patients with LS-HL, without B symptoms or mediastinal bulk, in an external independent cohort. Results were consistent between the RAPID cohort and the external H10 validation cohort across all analyses, with remarkably similar observed effect sizes. Although the association between conventional tumor bulk expressed as a binary variable and outcomes in HL is well established,[9,12,17] the largest prior study of MTD in LS-HL was a single-center, retrospective study (N = 185) with a heterogeneously treated cohort.[10] Our study is unique in 2 major respects. First, it uses prospective clinical data from 2 large, highly cited, phase 3 clinical trials featuring contemporary PET-adapted treatment. Second, the findings are applicable to the modern era for a favorable-risk, low–tumor-burden LS-HL population, in which few patients meet conventional definitions of "bulk."

A key finding was that increasing MTD correlated with higher risk of relapse as a continuous variable. Importantly, there was no stepwise threshold beyond which the relapse risk markedly increased. For patients treated with chemotherapy alone in this low–tumor-burden LS-HL population (without B symptoms or mediastinal bulk), a threshold of 5 cm performed marginally better than others based on the highest AUC value, although a similar effect size was seen using thresholds between 3 cm and 6 cm in this patient group. Another study of MTD in stage I/II HL that included patients with higher tumor burden (ie, patients with mediastinal bulk and B symptoms) suggested a higher threshold of 7 cm.[10] This indicates a continuum of increased risk with increasing MTD. If a binary cutoff is required for risk stratification, the optimal threshold will vary according to the patient population and the proposed intervention being investigated. A threshold of 5 cm is currently being evaluated for risk stratification in LS-HL in the RAFTING (www.ClinicalTrials.gov identifier: NCT04866654) clinical trial. In the future, a more nuanced approach would be to incorporate MTD values with other risk factors to create a personalized risk calculation, capable of informing discussions about the comparative risks and benefits of using radiotherapy in addition to chemotherapy in LS-HL. Such developments are beyond the scope of this study but will be essential in realizing the ultimate goal of achieving optimal tumor control with primary treatment while minimizing late consequences such as cardiovascular disease and second cancers.

By combining data from randomized trials comparing chemotherapy alone vs chemotherapy and radiotherapy, this study provides unique insights into the relevance of treatment modality. Both treatment modality (C vs CMT) and MTD were independently associated with risk of relapse in multivariable analyses, but there was no evidence of a differential effect for MTD between the 2 treatment groups. EFS rates for patients with both risk factors (ie, higher MTD and receipt of chemotherapy alone) were suboptimal. Although radiotherapy reduces this risk, it does not eliminate the impact of MTD, although the absolute difference in EFS rates for those with high vs low MTD for patients receiving CMT is small. Ongoing studies are evaluating whether MTD can be used to guide use of radiotherapy in LS-HL, including the RADAR clinical trial (www.ClinicalTrials.gov identifier: NCT04685616) in which, at investigator discretion, radiotherapy is permitted for those with who become PET negative after chemotherapy if their baseline MTD was ≥5 cm. An advantage of using a 5-cm threshold in this patient group is that it limits the use of radiotherapy and its associated risk of late effects (eg, second

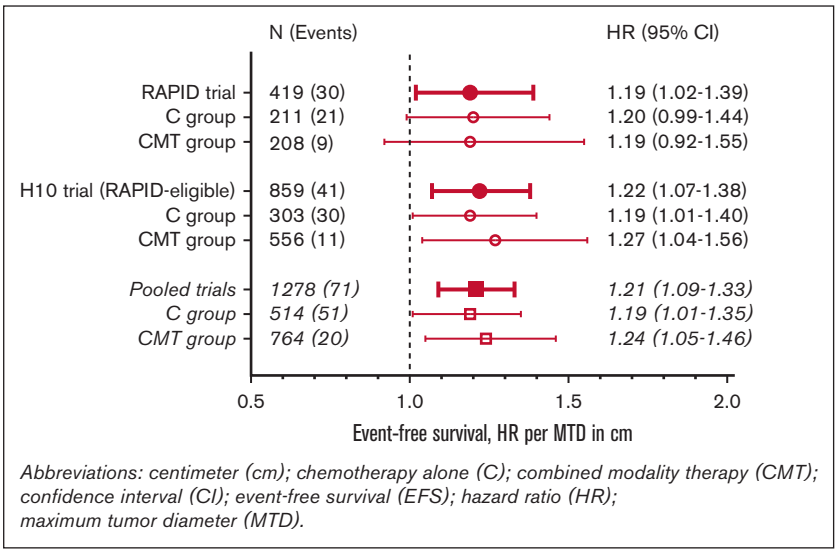


Figure 2. Forest plot showing the association between MTD (per centimeter) and EFS for patients achieving PET negativity. cm, centimeter.

Abbreviations: centimeter (cm); chemotherapy alone (C); combined modality therapy (CMT); confidence interval (CI); event-free survival (EFS); hazard ratio (HR); maximum tumor diameter (MTD).

malignancies and cardiovascular disease) to a relatively small proportion of higher-risk patients. Outside of clinical trials, radiotherapy consolidation should be considered for patients with higher MTD for whom the risk of late toxicity is not unacceptably high. A threshold <5 cm can be considered when the risks of radiotherapy toxicity are low.

There was no association between MTD and EFS in H10 patients who would not have been eligible for RAPID (ie, those with B symptoms and/or mediastinal bulk). This is unexpected given that the association between bulk and outcomes in HL has been observed in multiple studies, and mediastinal bulk is a well-validated adverse prognostic factor.[9,10] Noting that these findings require validation, 1 consideration is that mediastinal bulk can be heterogeneous, comprising a large solitary mass or multiple smaller or conglomerate nodes, so may not be reported consistently by trial sites, nor always correlate with MTD. The majority of these patients also have more widespread disease; therefore, the influence of a single dominant lesion may be less important. These findings mirror experience in advanced-stage HL, in which bulk is associated with higher rates of early PET positivity but is not an independent prognostic factor when considered alongside PET response.[18-20]

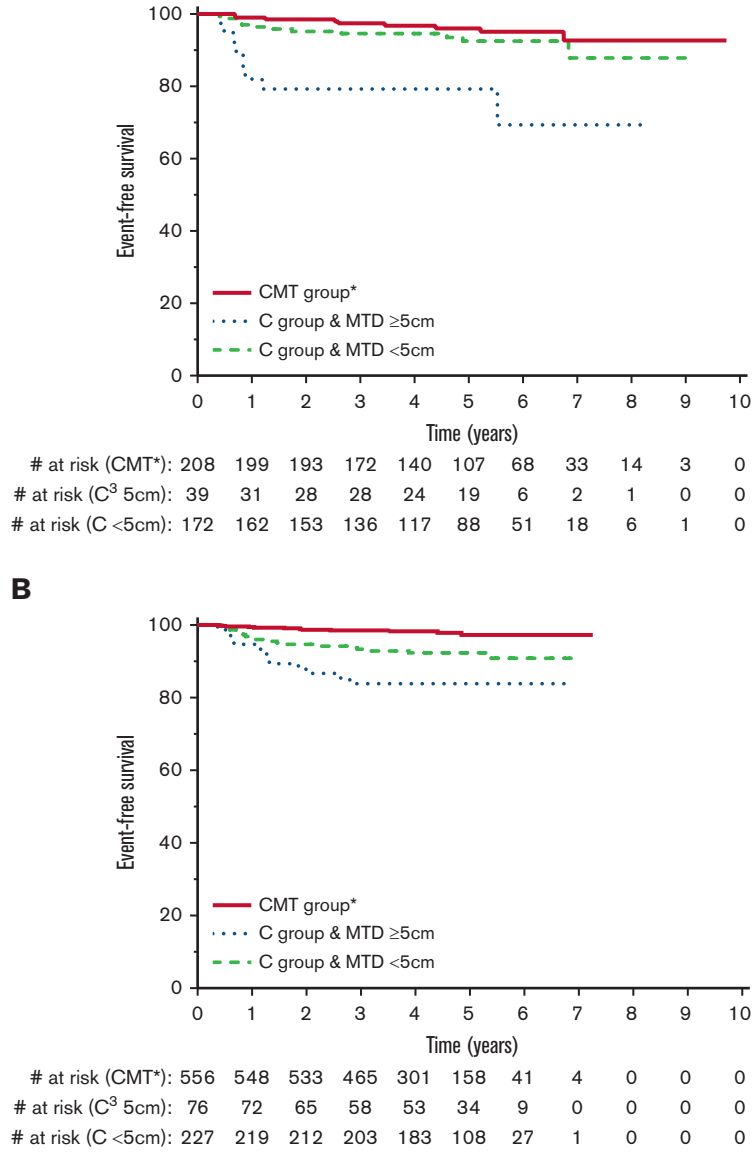
Table 3. Association between increasing MTD thresholds and EFS for patients achieving PET negativity treated with chemotherapy alone: pooled analysis of H10 subset with RAPID

MTD (cm) threshold*	<MTD threshold		≥MTD threshold		Effect ≥MTD threshold
	n	Events	n	Events	HR (95% CI)†, *P* value
1	20	2	494	49	0.98 (0.24-4.05), .977
2	74	5	440	46	1.61 (0.63-4.13), .319
3	191	10	323	41	2.63 (1.31-5.31), .007
4	309	20	205	31	2.55 (1.43-4.52), .001
5	399	30	115	21	2.65 (1.51-4.64), <.001
6	441	38	73	13	2.27 (1.21-4.28), .011
7	477	46	37	5	1.45 (0.57-3.64), .435
8	497	48	17	3	1.79 (0.56-5.77), .329
9	506	50	8	1	1.22 (0.17-8.84), .847
10	512	51	2	0	Not estimable
11	513	51	1	0	Not estimable
12	513	51	1	0	Not estimable
13	514	51	0	0	Not estimable

Showing data for N = 514 patients.
cm, centimeter.
*Small numbers of patients and events across some groups.
†Adjusted for trial cohort.

In this validation study, we did not receive data on outcomes for PET-positive patients in the H10 trial and therefore cannot comment on the association of MTD with EFS for the trial population as a whole. However, there was no association between MTD and EFS for PET-positive patients in the RAPID trial.[11] It is important to note that the definition of "PET negativity" in these trials did not encompass patients with a Deauville score of 3, who would now be considered to have achieved complete metabolic response by modern criteria.[14] Another limitation of this analysis is a lack of centralized radiology review and therefore we cannot guarantee that MTD was evaluated in coronal or sagittal as well as axial planes in all cases. However, we demonstrate that our findings are applicable to real-world radiology reporting and clinical practice, and are highly reproducible.

Baseline PET assessment was not mandatory in either RAPID or H10. Advanced PET metrics offer an alternative method of measuring tumor bulk. The most widely studied has been metabolic tumor volume (MTV), which provides a measure of overall tumor burden. MTV is associated with PFS in HL, including in patients with LS-HL recruited to the H10 trial.[7] Progress is being made toward standardization of MTV measurement, which should inform optimal thresholds for specific patient populations in the near future.[21] Whether measurement of overall tumor burden by MTV has a stronger association with prognosis than the diameter of the largest single lesion in LS-HL remains unclear and is currently



Abbreviations: centimeter (cm); chemotherapy alone (C); combined modality therapy (CMT); event-free survival (EFS); maximum tumor diameter (MTD).

Figure 3. Event-free survival according to MTD and treatment group. Kaplan-Meier plots of EFS by treatment group and MTD for patients achieving PET negativity in (A) RAPID and (B) H10 subset. *Evaluation of MTD thresholds was not possible in the CMT group because of low number of events.

under further investigation. For now, MTD is easily measured in routine clinical practice without the need for calibration of measurement against a benchmark, as for MTV.[22] The ongoing RADAR trial is evaluating MTD alongside MTV and other PET metrics simultaneously in a LS-HL population.

In conclusion, this international validation study confirms that increasing MTD is associated with shorter EFS in patients with LS-HL, without mediastinal bulk or B symptoms, who achieve PET negativity. Furthermore, MTD was an independent risk factor for disease relapse in this favorable-risk HL group. These findings can inform clinical discussions of risk for a personalized application of radiotherapy in LS-HL, particularly for patients not meeting classical bulk criteria, as well as the design of future clinical trials. Finally, we propose moving away from binary definitions of bulk to consideration of maximum tumor size as a continuous variable that confers greater risk of relapse as MTD increases, with integration of this into clinical decision making.

Acknowledgments

The authors thank the investigators, trial teams, positron emission tomography centers, patients, and their families from all participating countries for their support. The RAPID trial was run by the

Cancer Research UK and University College London Cancer Trials Centre. Central coordination of the H10 trial was performed by the European Organisation for Research and Treatment of Cancer (EORTC), and participation of Lymphoma Study Association centers was supported by the Assistance Publique des Hôpitaux de Paris.

S.F.B. acknowledges support from the National Institute for Health Research and Social Care (RP-2-16-07-001). This work was also supported by core funding from the Wellcome/EPSRC Centre for Medical Engineering at King's College London (WT203148/Z/16/Z). E.H.P., T.I., and J. Radford are supported by the National Institute for Health Research (NIHR) Manchester, Biomedical Research Centre. The RAPID trial (NCT00943423) was supported by the Leukaemia and Lymphoma Research Fund (now Blood Cancer UK), the Lymphoma Research Trust, Teenage Cancer Trust, and the UK Department of Health. The H10 trial (NCT00433433) was supported by EORTC (Belgium), Lymphoma Study Association (France), Fondazione Italiana Limfomi (Italy), Fondation Belge contre le Cancer (Belgium), Dutch Cancer Society (The Netherlands), Institut National Du Cancer (France), Assistance Publique des Hopitaux de Paris (France), Societe Française de Medecine Nucleaire et Imagerie Moleculaire (France), Associazone Angela Serra (Italy), van Vlissingen Lymfoom Fonds (The Netherlands), and Chugai Pharmaceutical (Japan).

The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health and Social Care.

Authorship

Contribution: E.H.P., N.C., and J.R. designed the research, analyzed data, and wrote the manuscript; and all authors performed research and approved the final manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: E.H.P., 0000-0001-9316-7544; N.C., 0000-0002-0688-9192; T.I., 0000-0003-3191-7324; I.A., 0000-0001-6175-4277; A.N., 0000-0003-2253-0427; S.F.B., 0000-0002-2516-5288; J.R., 0000-0001-7898-2786.

Correspondence: Elizabeth H. Phillips, Division of Cancer Sciences, University of Manchester and Manchester Cancer Research Center, The Christie Hospital, Unit 26, Wilmslow Rd, Manchester M20 4BX, United Kingdom; email: beth.phillips@manchester.ac.uk.

References

1. Fuchs M, Goergen H, Kobe C, et al. Positron emission tomography–guided treatment in early-stage favorable Hodgkin lymphoma: final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. *J Clin Oncol*. 2019;37(31):2835-2845.
2. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med*. 2015;372(17):1598-1607.
3. André MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: final results of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol*. 2017;35(16):1786-1794.
4. Henson KE, Reulen RC, Winter DL, et al. Cardiac mortality among 200 000 five-year survivors of cancer diagnosed at 15 to 39 years of age: the teenage and young adult cancer survivor study. *Circulation*. 2016;134(20):1519-1531.
5. Schaapveld M, Aleman BMP, van Eggermond AM, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. *N Engl J Med*. 2015;373(26):2499-2511.
6. Barrington SF, Phillips EH, Counsell N, et al. Positron emission tomography score has greater prognostic significance than pretreatment risk stratification in early-stage Hodgkin lymphoma in the UK RAPID study. *J Clin Oncol*. 2019;37(20):1732-1741.
7. Cottereau A-S, Versari A, Loft A, et al. Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial. *Blood*. 2018;131(13):1456-1463.
8. Raemaekers JMM, André MPE, Federico M, et al. Omitting radiotherapy in early positron emission tomography–negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol*. 2014;32(12):1188-1194.
9. Klimm B, Goergen H, Fuchs M, et al. Impact of risk factors on outcomes in early-stage Hodgkin's lymphoma: an analysis of international staging definitions. *Ann Oncol*. 2013;24(12):3070-3076.
10. Kumar A, Burger IA, Zhang Z, et al. Definition of bulky disease in early stage Hodgkin lymphoma in computed tomography era: prognostic significance of measurements in the coronal and transverse planes. *Haematologica*. 2016;101(10):1237-1243.
11. Illidge TM, Phillips EH, Counsell N, et al. Maximum tumor diameter is associated with event-free survival in PET-negative patients with stage I/IIA Hodgkin lymphoma. *Blood Adv*. 2020;4(1):203-206.
12. Bradley AJ, Carrington BM, Lawrance JA, Ryder WD, Radford JA. Assessment and significance of mediastinal bulk in Hodgkin's disease: comparison between computed tomography and chest radiography. *J Clin Oncol*. 1999;17(8):2493-2498.
13. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol*. 1989;7(11):1630-1636.
14. Cheson BD, Fisher RI, Barrington SF, et al; Alliance, Australasian Leukaemia and Lymphoma Group, Eastern Cooperative Oncology Group, European Mantle Cell Lymphoma Consortium, Italian Lymphoma Foundation, European Organisation for Research, Treatment of Cancer/Dutch Hemato-Oncology Group, Grupo Español de Médula Ósea, German High-Grade Lymphoma Study Group, German Hodgkin's Study Group, Japanese Lymphorra Study Group, Lymphoma Study Association, NCIC Clinical Trials Group, Nordic Lymphoma Study Group, Southwest Oncology Group, United Kingdom

National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.

15. Borchmann P, Plütschow A, Kobe C, et al. PET-guided omission of radiotherapy in early-stage unfavourable Hodgkin lymphoma (GHSG HD17): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(2):223-234.
16. Juweid ME, Stroobants S, Hoekstra OS, et al; Imaging Subcommittee of International Harmonization Project in Lymphoma. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol*. 2007;25(5):571-578.
17. Brockelmann PJ, Muller H, Casasnovas O, et al. Risk factors and a prognostic score for survival after autologous stem-cell transplantation for relapsed or refractory Hodgkin lymphoma. *Ann Oncol*. 2017;28(6):1352-1358.
18. Kobe C, Goergen H, Baues C, et al. Outcome-based interpretation of early interim PET in advanced-stage Hodgkin lymphoma. *Blood*. 2018;132(21):2273-2279.
19. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med*. 2016;374(25):2419-2429.
20. Casasnovas R-O, Bouabdallah R, Brice P, et al. PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study. *Lancet Oncol*. 2019;20(2):202-215.
21. Meignan M, Cottereau A-S, Specht L, Mikhaeel NG. Total tumor burden in lymphoma – an evolving strong prognostic parameter. *Br J Radiol*. 2021;94(1127):20210448.
22. Barrington SF, Cottereau A-S, Zijlstra JM. Is ^{18}F-FDG metabolic tumor volume in lymphoma really happening? *J Nucl Med*. 2024;123:267022.